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(54) Title: NON-GELATIN BASED CAPSULES

(57) Abstract: A capsule for a complementary health or pharmaceutical product comprising: (a) a hard or soft shell made from a gelatin free material; and (b) a fill material; wherein the shell material comprises a suitable polymer or gum, or a combination of two or more polymers and/or gums having a hydrophilic/hydrophobic balance determined by water solubility which is compatible with the fill material, and/or the appropriate chemical characteristics to minimise chemical interactions with the fill material components.

NON-GELATIN BASED CAPSULES

This invention relates to non-gelatin based capsules and compositions useful for the manufacture of shells for such capsules. More specifically, it relates to compositions useful for the manufacture of soft or hard shells specifically used to encapsulate complementary health products such as vitamin, mineral, herbal extracts, nutrient and probiotic compositions, pharmaceutical products and other therapeutic compositions. The invention also relates to novel capsules and to methods of manufacturing such capsules.

The invention particularly relates to the use of a combination of natural, semi-synthetic and synthetic polymers and gums to form a shell for a soft or hard shell capsule.

Traditionally, both soft and hard shell capsules have been manufactured using gelatin, particularly mammalian gelatin as a material of choice. Whilst gelatin has some preferred technical and manufacturing characteristics as a polymeric system to be used in the manufacture of capsules, it is subject to a number of limitations in its use. These include its relatively high hydrophilic character which facilitates the migration of hydrophilic ingredients included in the fill material into the shell material containing gelatin; its chemical reactivity with fill ingredients containing, for example aldehyde functional groups; and its ability to react with various plasticiser components such as glycerol in the shell either directly or after oxidation of these plasticisers. Attempts to overcome these difficulties have included changing the solubility character of the fill ingredients by choosing a different salt or derivative; use of succinated gelatin; and the use of a less reactive plasticiser such as sorbitol. Although these modifications have alleviated some of the difficulties associated with the use of gelatin, there has been a move away from the use of animal products such as mammalian gelatin leading to the development of non-gelatin based capsules.

Shells based on carrageenan as the sole polymer are not readily formed into a workable capsule as the melting temperature of the carrageenan shell material is very close to that of the sealing temperature. At concentrations that are needed to make a good film for making capsules, the carrageenan system can not be readily mixed. This is overcome by adding large amounts of water to the carrageenan system which, then has to be removed from the cast film by freezing. This then leads to a drier film, which is very tough to seal. Hence simple carrageenan based capsules are not workable. It does not matter what type of carrageenan (Iota, Kappa or Lambda) either on their own or in combination are used as the base, they all suffer from this non-working characteristic. In general, these problems occur irrespective of the film material used in any capsules formed by these simple polymer systems.

Australian patent 735699 to R.P. Scherer Technologies Inc., discloses hard and soft capsules formed by the combination of a modified starch and Iota-carrageenan. This document addresses the processing difficulties associated with the use of carrageenan based capsules and discloses that the combination of modified starch and Iota-carrageenan is suitable for ease of forming a capsule, particularly utilising a rotary die process.

Capsules based on starch are described in, for example, PCT/CH00/00616 to Peter Greither. Capsules based on starch and starch derivatives are extremely sensitive to moisture, hence they have to be packed in an expensive water resistant packaging such as a blister platform made with a film material with a very low water vapour transmission rate. Such film material is very hard to work with in manufacturing. As bottles are generally opened and closed repeatedly, starch based capsules will pick up moisture very easily if housed in a bottle and go soft and so bottles cannot be used. The flexibility, hardness and seam stability of such capsules are very moisture dependent. The degree of moisture sensitivity is about the same or slightly greater than that of gelatin based capsules.

Starch capsules are also temperature sensitive in that at below 5°C, they can go brittle while at above 40°C (especially at greater than 25% relative humidity) they go very soft.

The extent of interaction of the fill ingredient with starch based shells is very dependent on the water content of the shell. Hence, such relatively hydrophilic starch shells, even if formed, are not readily worked as a health product given the difficulties associated with matching the fill ingredient to the shell. Many other similar polymer or other material based systems (other than gelatin) suffer from these types of problems leading to the same inability to form a stable encapsulated product as for the starch based shell.

To overcome these difficulties, various additives have to be included into the shell formulation to assist in formation of a stable capsule. For example, glyceryl monostearate may be added to provide some internal slip or mold release ability for the components in the mixture that will make the shell. However, such agents like glyceryl monostearate produce a hazy capsule which prevents ready acceptance by consumers.

Syrups, such as sorbitol or maltitol based additives have also been used. These components are sugar based and prevent the capsule from being designated as a "sugar free" capsule. Any water in the shell will be readily attracted to the sugar type polyols and the shell will lose flexibility and go hard. If environmental moisture is present, the shell will readily pick up moisture and go soft. This extreme moisture sensitivity makes these capsules physically unstable.

Hence the use of these types of additives, whilst reducing the difficulties in working particular systems based on a variety of polymers either on their own eg starch based polymers, or a combination of polymers eg hydroxypropylstarch and polyvinylalcohol, have inherent difficulties in themselves so they do not contribute to forming a marketable capsule.

An example of the inherent difficulty with the prior art based on non-gelatin capsules, is that the capsules tend to become unstable particularly when encapsulating hydrophilic materials or materials that can absorb water from the shell. Starch based shells, which are relatively hydrophilic in nature, draw moisture both from the fill material and the surrounding atmosphere and tend to become unstable.

A focus on the process of the encapsulation manufacturing steps in the prior art essentially ignores the interaction of the shell with the fill material and with the environment. This focus also ignores the problems of selecting the components of the shell to match the characteristics of the fill materials.

The above discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

Throughout the description of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, integers or process steps.

The present invention aims to overcome or at least alleviate one or more of the difficulties associated with the prior art.

The present invention provides for a shell composition which will allow for the formation of a stable capsule suitable for encapsulating a broad range of fill materials. This includes both oil soluble and water soluble solutions and semi solids. It has been found that providing a shell with the appropriate hydrophilic/hydrophobic balance and/or chemical character for the fill material to be encapsulated, will result in a stable capsule.

According to a first embodiment of the invention, there is provided a capsule for a complementary health or pharmaceutical product comprising:

(a) a hard or soft shell made from a gelatin free material; and

(b) a fill material;

wherein the shell material comprises a suitable polymer or gum, or a combination of two or more polymers or gums having a hydrophilic/hydrophobic balance as determined by water solubility which is compatible with the fill material, and/or the appropriate chemical characteristics to minimise chemical interactions with the fill material components.

By describing the shell material as having a hydrophilic/hydrophobic balance which is compatible with the fill material, or that the shell material has appropriate chemical characteristics to minimise chemical interactions with the fill material components, we mean that the shell material should be selected to avoid notable interaction between the fill material and the shell material. That is, the shell material should be selected based on its hydrophilicity/hydrophobicity or chemical characteristics that prevents, or at least minimizes to a substantially non-detectable extent, migration of the fill material into the shell material or chemical reaction between the fill material and shell material which can cause instability of the capsule.

The hydrophilic/hydrophobic balance between the shell material and the fill material is determined by a measure of the water solubility of each component. In reference to the hydrophilic/hydrophobic nature of the "fill material" as used in the description and claims, we are referring to the nature of the particular component of the fill material which is susceptible to migration into the shell, or may react with components of the shell material. The component may well be the sole component, or be applicable to a single component, or a number of components in a mixture of active components that is to be encapsulated. The fill material is usually dissolved, suspended or emulsified with an excipient carrier.

In general, the invention has particular applicability to the encapsulation of complementary health products including vitamin, mineral, herbal extracts, nutrient and probiotic compositions. The development of the invention does however, also have applicability to other therapeutic compositions such as pharmaceutical products in general, inclusive of prescription and non-prescription pharmaceutical compositions, where in general the active may also be susceptible to migration into, or chemical interaction with the shell material components.

In order for the hydrophilic/hydrophobic balance between the shell material and the fill material to be compatible, there should be a difference in the percentage of water solubility between the shell material and the fill material of a factor of at least 2, preferably at least 10.

In a particular embodiment, the fill material is relatively hydrophobic having a water solubility of less than 0.5% and the polymer or gum or combination of polymers and/or gums of the shell material is hydrophilic in nature having a water solubility of between 2 and 100%.

In yet a further particular embodiment, the polymer or gum or combination of polymers or gums forming the shell material is hydrophobic having a water solubility of less than 0.5%, and the fill material is relatively hydrophilic having a water solubility of between 2 and 100%.

Preferably, migration of the fill material into the shell material is maintained at less than 5% over a period of 30 days. That is a partition co-efficient of less than 0.05. More preferably the partition co-efficient is less than 0.01, and most preferably less than 0.005.

The active component of the fill material such as a complementary health product is generally dissolved, suspended or emulsified in an excipient carrier, whether that be an aqueous miscible agent or oil based agent. It is generally the hydrophilic/hydrophobic character or chemical characteristics of the active components of the fill material which influences the selection of the shell material. As a general rule, the excipient carrier is unlikely to migrate into the shell material or react with the shell material components.

Nevertheless, the hydrophilic/hydrophobic character of the excipient carrier is also taken into account when selecting the appropriate shell material, however the shell material will generally be selected based on the hydrophilic/hydrophobic nature of the migratable ingredient , which is generally the active product or a component of the active product in, for example a complementary health composition.

It has been found that when the hydrophilic/hydrophobic nature based on a determination of the percentage water solubility of the migratable component of the fill material, and the shell material differs by a factor of at least 2, problems associated with migration of the fill material into the shell and/or shell stability are substantially avoided.

Generally, the active components will be dissolved in a compatible excipient carrier, for example an aqueous soluble active material will be dissolved in a water miscible agent. However, many instances arise wherein a water soluble active such as water soluble vitamin may be suspended in an oil based agent. Generally, the selection of the compatible shell material will be based on the water solubility of the active component in this case, although the selection of the shell material is somewhat balanced to accommodate the hydrophilic/hydrophobic nature of the oil based excipient carrier.

The solubility of migratable active components forming the fill material and the components of the shell material in solvents such as water is readily determined by the skilled practitioner. It is on this basis that appropriate selection of the polymers and/or gums used to make the shell material can be determined based on the relative solubility of the fill material and the materials used to form the shell. The extent of partitioning of the fill material into the shell material is determined by the relative solubility of the fill material in the excipient carrier and the shell material.

It is preferred that the equilibrium co-efficient between the shell and the fill material should be less than 0.05 and most preferably less than 0.01 so that insignificant amounts of the fill material partitions between the excipient carrier and the shell. Instead of measuring this partitioning for each active between the excipient carrier and each possible shell material, it has been found that with appropriate selection based on the water solubility of the polymer material and the fill material, it is possible to form a stable capsule rather than making a determination based on the solubility of the active in solvents such as water or oil.

The polymer or gum of the shell material may be selected from any natural semi synthetic or synthetic polymer or gum material depending on the marketing position of the capsule as well as manufacturing considerations. The polymer or gum may also be selected on the basis of their hydrophilic/hydrophobic character as shown by their solubility in water.

Combinations of polymers or gums can be chosen to fine tune this hydrophilic/hydrophobic character. A further selection criterion may be the ability of the polymer or gum or the combination of polymers or gums to not chemically interact with the components of the fill material.

Preferred natural gums or polymer products to form the shell material can be grouped in terms of their relative water solubility. Those skilled in the art will be able to use the differences in water solubility of particular grades of the particular natural gum or polymer to fine tune the balance position. Table 1 shows such a grouping.

Table 1: Grouping of preferred natural gums or polymers based on relative water solubility.

Relative Water Solubility		
Lower	Mid	Higher
Tragacanth	Karaya Gum	Ghatti Gum
Locust Bean Gum	Carrageenan	Guar Gum
Psyllium Seed Gum	Pectin	Algin
Quince Seed Gum	Starch	Xanthan Gum
Agar	Dextrins	
Furcellaran		

Preferred modified or semi synthetic gums or polymers can be grouped in terms of their relative water solubility. Those skilled in the art will be able to use the differences in water solubility of particular grades of the particular modified or semi synthetic gum or polymer to fine tune the balance position. Table 2 shows such a grouping.

Table 2: Grouping of preferred semi synthetic gums or polymers based on relative water solubility.

Relative Water Solubility		
Lower	Mid	Higher
Ethyl Cellulose	Hydroxypropylcellulose	Carboxymethylcellulose
Microcrystalline Cellulose	Hydroxyethylcellulose	Methylcellulose
Carboxymethyl Locust Bean Gum	Hydroxypropylstarch	Hydroxypropylmethylcellulose
	Hydroxyethylstarch	Ethylhydroxymethylcellulose
	Low Methoxypectin	

Preferred synthetic gums or polymers can be grouped in terms of their relative water solubility. Those skilled in the art will be able to use the differences in water solubility of particular grades of the particular synthetic gum or polymer to fine tune the balance position. Table 3 shows such a grouping.

Table 3: Grouping of preferred synthetic gums or polymers based on relative water solubility.

Relative Water Solubility		
Lower	Mid	Higher
Polymethylacrylates	Polyvinylpyrrolidine	Ethylene Oxide Polymers
	Polyvinylalcohol	Poloxamer
	Carboxyvinylpolymer	
	Carbomer	

Preferred shell materials for use in the present invention include one or a combination of components selected from those listed in the Tables above. A relatively hydrophobic shell material can be achieved with the selection of one or a combination of two or more polymers or gums from the mid to higher relative water solubility list, while relatively hydrophobic shell materials can be achieved with the selection of one or a combination of two or more polymers or gums from the mid to lower relative water solubility list. Combinations will be used to achieve appropriate hydrophilic/hydrophobic characteristics for the shell material to encapsulate any particular fill material.

Similarly, the components of the fill material of such capsules can be classified by their water solubility or chemical reactivity characteristics. Suitable complementary health fill materials each of which may be considered to be

migratable complementary health products, as each has the potential to migrate into non-compatible shell materials over time, include:

(i) Oil soluble vitamins including single vitamins such as vitamin E (either as the alcohol or the corresponding ester), d-l alpha tocopherol or d-alpha tocopherol in various strengths; Vitamin A, Betacarotene, Vitamin A&D either synthetic or sourced from Cod Liver Oil or other fish oils such as Halibut Oil, Fish oils as a source of EPA or DHA;

(ii) Water soluble vitamins such as vitamin B1, B2, B6, B12, vitamin C, nicotinamide either in combination such as B group Vitamin formulations, stress formulation in combination with vitamins and minerals, or other nutrients as in multivitamin and mineral formulations, such as antioxidants;

(iii) Vitamin combinations, for example vitamins combined with minerals and nutrients such as salts of calcium and magnesium, potassium sulphate, salts and/or chelate of iron, copper chromium, zinc and manganese etc. Nutrients such as biotin, choline bitartrate, inositol;

(iv) Vitamins combined with herbs such as all forms of garlic, saw palmetto, Echinacea, ginger, grape seed, ginkgo biloba, ginseng, dong quai, green tea, celery seed, papaya, liquorice root etc;

(v) Herbal combinations;

(vi) Fatty Acids such as Omega 3, Omega 6 fatty acids derived from Evening Primrose oil, flaxseed oil, tuna oil, olive oil, fish oils or fatty acids in combination with vitamins and/or herbal or other nutrients;

(vii) Single or combination nutrients and enzymes such as Coenzyme Q10 and glucosamine, and lecithin either as single ingredient or as an excipient;

(viii) Chemically reactive ingredients such as ascorbic acid, phenolic compounds such as polyphenols and tannins in herbal extracts such as grapeseed, aldehydic compounds or reducing sugars such as flavouring agents such as glucose, peroxides such as found in fish or vegetable oils, heavy metals such as chromium salts, gelling agents such as calcium or potassium salts.

The choice of shell material will largely depend upon the nature of the fill material. With components of the fill material that have a high water solubility, the shell should comprise either a hydrophobic polymer or gum, ie one or more polymers or gums selected from the low to mid relative water solubility, or a combination of polymers or gums that lead to a composition that is hydrophobic in nature. With appropriate matching of the shell material to the fill material, a stable capsule may be formed in such a manner, the most appropriate shell composition can be chosen to match the fill material to be encapsulated by the shell.

In a preferred embodiment, the shell material includes at least a relatively hydrophobic polymer such as carrageenan together with a controlled amount of a secondary polymer with a controlled extent of hydrophilicity such as a modified starch or hydroxypropylmethylcellulose. The carrageenan base can incorporate different proportions of lota, Kappa and Lambda carrageenan. This product is of relatively balanced hydrophobic character and has been found to be stable, even in the presence of water soluble fill materials due to the hydrophobic character of the shell. It has particularly been found that capsules produced from a shell having two or more polymeric materials has enhanced moisture stability. The balanced character of the carrageenan/secondary polymer shell ensures that the water content of the shell remains relatively stable upon storage.

In a further preferred form of the invention, the composition comprises the combination of carrageenan together with a secondary hydrophilic polymer such as hydroxypropylstarch. Preferred amounts of carrageenan range from about 6 to 12% by weight of the wet shell composition during formation. Preferably the preferred ratio between the carrageenan and the second polymer ranges from 1:1 to about 1:4.

The capsules of the present invention also have enhanced fill ingredient stability. The inherent hydrophobic character of the shells in this particular

example means that there will be less migration of water soluble ingredients into the shell from the fill material. There will also be less absorption of moisture from the surroundings, meaning that the capsules will remain stable, even if stored in bottles and the like. This means that there will be less degradation and longer shelf life.

Oil soluble ingredients do not tend to migrate from the fill to the shell and generally do not suffer from the same type of stability problem, however to avoid any problem, it has been found that with the use of a shell material with appropriate hydrophilic/hydrophobic balance, migration of oil soluble ingredients can be avoided.

Such a shell can also be used to encapsulate chemically reactive fill components such as aldehydic molecules because there is no possibility of a pellicle forming Maillard reaction occurring. Such chemical reactions, for example, the reaction between amino groups and aldehyde groups, or polyphenols and alcohols can occur slowly. Standard tests during initial product development may not show that a problem with such chemical reactions is occurring. It is not always possible to predict that a reaction might occur in any particular combination of fill material and shell material, however, with the ability to use polymers and/or gums other than the traditional gelatin type, a range of chemical options are greatly expanded. Hence when polymers are being chosen based on the hydrophilic/hydrophobic balance, wherever there is a potential chemical interaction possible, an alternative polymeric system with the same solubility characteristics is chosen.

Another preferred embodiment of the invention includes a shell made by using cellulose derivatives such as hydroxypropylcellulose in combination with a secondary polymer or gum such as guar gum. This shell has a much more hydrophilic character than the carrageenan based embodiment and so is suitable for use with hydrophobic fill components, for example oil soluble herbals such as Saw Palmetto. Whilst, such a capsule will need to be stored in suitable containers to prevent excessive uptake of moisture from the

environment, migration of the fill components into the shell can be well controlled.

Gelatin free shells for capsules formed in accordance with inventions described herein provide the following previously unknown or unexpected advantages:

(i) Any water soluble vitamins in the fill material does not unduly or unexpectedly migrate into the shell where they can degrade and/or polymerise leading to shell discoloration;

(ii) Any microbiological contamination would not grow on the shell. Microbiological contamination may be expected on some moisture sensitive capsules, such as the starch based capsules or the hydroxypropylmethylcellulose based capsules;

(iii) The shell retains its inherent softness without the need for further additives such as syrups. The shell retains elasticity, flexibility and burst strength;

(iv) The disintegration time of a capsule in accordance with the invention is consistent unlike that of other capsules where the disintegration time will vary dependent upon the moisture content and as the shell hardens.

(v) The shells in accordance with the invention have enhanced clarity as there is no need for the addition of glycerol monostearate. The shells are also sugar free as there is no requirement for sugar polyol additives.

In a further embodiment, the present invention resides in a process for producing a capsule having a gelatin free shell; the processing comprising:

(a) providing a complementary health fill material for encapsulation which has been classified by its hydrophilic/hydrophobic balance as determined by water solubility, or chemical reactivity characteristics;

(b) forming a shell material from a suitable polymer or gum, or a combination of two or more polymers and/or gums, wherein the shell material is selected such that the hydrophilic/hydrophobic balance and/or chemical characteristics of the shell material is compatible with hydrophilic/hydrophobic

and/or the chemical characteristics of the complementary health fill material to minimise chemical interaction with the fill material components; and

(c) encapsulating the complementary health fill material within the shell material.

The capsules may be formed by conventional rotary die processes. Such processes include casting ribbon material either using conventional casting method or using extrusion or gravity feed of a liquid polymer/gum material onto a revolving casting or forming drum.

The shell formulations are generally provided to the drum at a temperature just above the melting point of the formulation. For example for the carrageenan/starch based shell described in Australian 735699 to R P Scherer Technologies, this temperature range is disclosed as 2 to 5^0C. The temperature will vary according to each specific shell formulation. The fill material is provided to a hopper connected to a rotary die encapsulation machine. The hopper can be heated and jacketed. Encapsulation of the fill material between the ribbons of the film is generally carried out in accordance with conventional encapsulation procedures.

The preferred compositions also include a plasticizer. Suitable plasticizers include the materials used for the same purpose in gelatin based capsules. Representative plasticizers may be selected from polyhydric alcohols such as glycerol, sorbitol (if a sugar claim is not a problem), propylene glycol, polyethylene glycol and the like. The plasticizers may be employed in amounts up to 60 weight % of the dry shell composition or 30 weight % of the wet shell composition.

Most preferably, the plasticizers are used in an amount of from 10 to 25% weight based on the wet shell composition and 30 to 50% by weight of the dry cell composition.

Optionally, the shell composition may also include preservatives and stabilizers such as mixed parabens, ordinarily methyl or propyl parabens. The parabens may be incorporated in an amount of from 0 to 0.2 weight % of the wet shell and 0 to 0.4 weight % of the dry shell. Preservatives in general are unlikely to be required as in most forms, the selection of polymers used in accordance with the invention are unlikely to support microbial growth, unlike shell based on high proportions of starch or modified starches.

It is also preferred to use a buffer system in the composition. Any known buffer can be used with phosphate buffers being preferred.

Controlling the pH of the melt and film is desirable with formulations encorporating carrageenan as carrageenans are rapidly broken down in conditions of high temperature and acidity. Additionally, controlling the pH enables control of the gelling characteristics of the polymeric system to be controlled.

It is also preferred to control the amount of electrolytes by for example the addition of calcium ions which has an effect on the gelling characteristics of alginates.

The present invention will now be described with reference to the accompanying examples. These example are intended to be illustrative of the invention and the scope of the invention should not be considered to be limited to the embodiments described herein.

Example 1. The use of a single more hydrophobic material in the shell of a capsule containing more hydrophilic fill components.

Hydrophilic fill components include water soluble vitamins such as the B group and Vitamin C. B group vitamins such as 25 mg of Thiamine Nitrate, 15 mg of Riboflavine, 25 mg of Pyridoxine Hydrochloride and 20 mg of Nicotinamide can be combined with 100 mg of Ascorbic Acid as fill components

of a Complementary Health Care Product. This blend of water soluble vitamins is readily suspended in suitable vegetable oils such as soy bean oil using wax mixtures as the suspending agent and lecithin as the dispersing agent according to the following formula.

		Water Solubilities
Thiamine Nitrate	25 mg	2.7%
Riboflavine	15 mg	0.5%
Pyridoxine Hydrochloride	25 mg	22%
Nicotinamide	20 mg	100%
Vitamin C	100 mg	33%
Wax Mixture	60 mg	less than 0.001%
Lecithin	15 mg	dispersing agent
Soy Bean Oil	279 mg	less than 0.001%

These components would traditionally be used with a gelatin based gel capsule. However, it has been found that particularly with those compounds that have a water solubility greater than 2%, such as Thiamine Nitrate, Vitamin C, Pyridoxine Hydrochloride and Nicotinamide, that they migrate into relatively hydrophilic materials such as a gelatin based shell capsule. It has been found that with the presence of such migratable fill materials that the shell materials best suited to encapsulate such migratable complementary health fill materials are drawn from those polymers and gums that have a lower water solubility. Materials suitable to encapsulate such a fill material would include furcellaran which disperses in water but does not dissolve to more than 0.05%, polymethacarylates which also has very low water solubility of less than 0.05% and ethyl cellulose, which, has a lower water solubility and variable dependent on degree of subsitution, but is generally is less than 0.001%.

A 5 % dispersion of furcellaran in water, plasticised with 30 % glycerol is used to cast a ribbon in a conventional rotary die soft capsule encapsulation machine and then used to encapsulate the suspension of hydrophilic vitamins described above. Non coloured, non opacified capsules are then produced.

Colouring and opacifying agents can be added in the same way as for gelatin based shells. For example, 3 g of Red Iron Oxide and 3 g of Yellow Iron Oxide can be blended into each kilogram of the furcellaran/glycerol aqueous dispersion to create a brownish opaque shell mass suitable for encapsulation of fill material which includes the water soluble vitamins above. Coloured, opacified capsules can then be produced.

These capsules are then dried in the conventional manner before being packed into suitable market packs.

When capsules made with this fill material and a gelatin based shell are stored at 30^{0}C for 6 months in amber glass bottles, the water soluble vitamins migrate from the fill material into the shell. When the shells of these gelatin based soft capsules are examined, it was found that they have discoloured due to the oxidation of the Vitamin C and the build up of the coloured B group vitamins.

On the other hand with capsules made with this fill material and a furcellaran based shell, there is significantly less discolouration indicating a reduced extent of migration of the vitamins into the shell.

Example 2. The use of a combination of more hydrophobic materials in the shell of a capsule containing more hydrophilic fill components.

Using the fill material in the above example, a capsule can be formed in the same way using a ribbon made from a blend of two or more such hydrophobic materials. For example a ribbon can be formed using a combination of;

1.0 %	Ethyl cellulose
10.0 %	Microcrystalline Cellulose
5.0 %	Glycerol
84.0 %	Water.

The water solubility of both the ethyl cellulose and microcrystalline cellulose is very low, less than 0.001%. If such capsules are made and stored as in Example 1, the shell discolouration is less than for the gelatin based soft capsule given in Example 1.

Example 3. The use of more hydrophilic shells in combination with more hydrophobic fill components.

Hydrophobic fill components include the standardised marker compound in a herbal extract such that the marker compound has a relatively low water solubility. The hypericin in hypericum extract has a low water solubility of around 0.005%. However, for formulation and clinical reasons, this type of active component may have to be formulated with a hydrophilic fill material carrier such as Polysorbate 80 which is fully miscible/dispersable with water. Such a typical fill formulation is given below:

Hypericum Extract standardised to contain 0.3 % hypericin	167 mg
Suspending agent	56 mg
Polysorbate 80	330 mg

The selection of the shell material is based on the hydrophobic nature of the complementary health fill material component. Oily fill components such as Vitamin D also have a low water solubility of about 0.001%. Vitamins of this type can be encapsulated either as simple oily solutions or as part of a combination multi vitamin and/or mineral and /or herbal system.

The shell materials best suited for such a hydrophobic type of key complementary health fill material components would be drawn from one or more of those polymers and gums that have a higher water solubility. Such polymers and gums include algin, guar gum, hydroxypropylmethylcellulose and ethylene oxide polymers.

For example a blend of

Hydroxypropylmethylcellulose	7 %
Polyethylene Glycol 400	2%
Water	91 %

The water solubility of hydroxypropyl methyl cellulose is around 9% depending on temperature and grade. Polyethylene glycol is fully water miscible. This combination of polymers and gums can be used to cast a ribbon in a standard rotary die encapsulation machine suitable for encapsulating oily focussed fill materials as exemplified above. Hence 553 mg of the fill material described above containing the hypericum extract can be encapsulated into an 11 oblong die on a standard rotary die encapsulation machine using a hydroxypropylmethylcellulose (HPMC) ribbon formulated as above. The capsules are then dried in the conventional manner before packing into suitable market packs.

When the extent of migration of the oily component in the fill material in the HPMC based soft capsule is compared to that in a comparative standard gelatin based shell, there is less migration for the HPMC based soft capsule.

Example 4. The use of shell components that do not react chemically with components in the fill material.

Aldehydic groups in molecules within the fill material can chemically react with amino groups in molecules that make up the shell polymers or gums forming crosslinked material on or within the polymer or gum. This crosslinked material will then not disintegrate and so the capsule cannot release its contents. Hence polymers and gums are chosen so that they do not contain such amino groups.

Many herbal extracts contain such an aldehydic group. Almond extract can contain benzaldehyde. The shell materials best suited for such a reactive fill material would be drawn from those polymers and gums that do not contain such an amino group. Such polymers and gums could include furcellaran, ethylcellulose and modified starches such as hydroxypropylstarch.

To show the way such polymeric and gum based shells have a reduced extent of chemical reaction when compared to standard gelatin based soft capsules, increasing amounts of formaldehyde were added to a fill material containing Polyethylene Glycol 400.

The soft capsules had shells which were either:

Polymer based containing	Hydroxypropylstarch
	Furcellaran
	Glycerol
	Water
or Gelatin based containing:	Gelatin
	Glycerol
	Water

After storage for 6 months at 30^{0}C in amber glass bottles, the rupture times of the shells were measured. These rupture times are recorded in the following Table.

PPM of Formaldehyde added to the fill material	Rupture time (mins) for polymer based shells	Rupture time (mins) for gelatin based shells
0	2.0	4.1
50	2.0	10.0
100	3.0	>30
200	3.0	>30

Example 5. The use of hydrophobic shells to reduce the uptake of water from the environment.

Capsules with varying hydrophobicity character can be made using different polymers. The hydrophobicity of the shell containing different polymeric and other materials increases in the order HPMC, starch, gelatin, furcellaran, When shells based on these different ingredients are stored in increasing relative humidity conditions, the water content of the shell also increases but at different rates dependent on the composition of the shell. This relative adsorption data is shown in the following Table.

% Relative Humidity of storage	Resultant % water content in shells using			
	HPMC	Starch	Gelatin	Furcellaran
10	6.1	4.9	2.8	2.0
20	9.8	7.5	4.0	3.0
30	12.5	11.1	5.4	4.1
40	15.3	13.0	7.5	6.0
50	20.1	16.1	9.9	8.2
60	25.0	20.8	13.2	11.9
70	33.0	25.9	18.2	15.4

Example 6. The use of shells with low water content to prevent migration of water in the fill material containing hydrophobic ingredients.

When hydrophilic fill materials such as herbal extracts based on carriers such a maltodextrin or alternatively hydrophilic fill liquids such as Macrogol 400 are used with shells that contain water, the water can migrate from the shell into the fill. This causes increased internal pressure in the soft capsule which combined with the increased shell brittleness due to the loss of water causes the soft capsules to sweat and in the extreme crack. Conventionally this issue is addressed by changing the plasticizer in the shell. This can cause shell haziness or the use of materials that are not well accepted by consumers or regulatory agencies.

However, by changing the polymer(s) and/or gum(s) used as part of the shell composition to a shell material which is hydrophobic in nature, the initial water content can be selected to be compatible with the type of fill material used.

Hence when soft capsules based on various materials and using PEG 400 as the hydrophilic fill are stored at 35^{0}C for six months, the degree of sweating and shell hardness is reduced in those shells in which hydrophobic shell ingredients are used.

Shell based on	Relative extent of sweating (the more stars, the more sweating)
Furcellaran	None seen
Gelatin	*
Starch	**
Ethylcellulose / hydroxypropylcellulose	***
Hydroxypropylmethylcellulose	***

The above description is intended to be illustrative of the preferred embodiments of the present invention. It should be understood that any modification without departing from the spirit or ambit of the invention is also incorporated herein.

Claims:

1. A capsule for a complementary health or pharmaceutical product comprising:
   (a) a hard or soft shell made from a gelatin free material; and
   (b) a fill material;

wherein the shell material comprises a suitable polymer or gum, or a combination of two or more polymers and/or gums having a hydrophilic/hydrophobic balance determined by water solubility which is compatible with the fill material, and/or the appropriate chemical characteristics to minimise chemical interactions with the fill material components.

2. A capsule according to claim 1 wherein the fill material comprises one or more vitamin, mineral, herbal extracts, nutrient or probiotic complementary health products.

3. A capsule according to claim 1 wherein the water solubility, as determined by the percentage water solubility, of the shell material and the migratable component(s) of the fill material differs by a factor of at least 2.

4. A capsule according to claim 1 wherein the water solubility, as determined by the percentage water solubility, of the shell material and the migratable component(s) of the fill material differs by a factor of at least 10.

5. A capsule according to claim 1 wherein the hydrophilic/hydrophobic balance and/or chemical compatability between the shell material and fill material is such that the equilibrium partition co-efficient is less than 0.05.

6. A capsule according to claim 1 wherein the hydrophilic/hydrophobic balance and/or chemical characteristic compatibility between the shell material and fill material is such that the equilibrium partition co-efficient is less than 0.01.

7. A capsule according to claim 1 wherein the polymer and/or gum is selected from any natural, semi synthetic or synthetic polymer and/or gum.

8. A capsule according to claim 1 wherein;

(a) the migratable component(s) of the fill material is/are relatively hydrophilic having a water solubility of between 2% to 100%; and

(b) the polymer or gum or the combination of polymer(s) and/or gum(s) of the shell material is a relatively hydrophobic material having a water solubility of less than 0.5%.

9. A capsule according to claim 1 wherein;

(a) the migratable component(s) of the fill material is/are relatively hydrophobic having a water solubility of less than 0.5%; and

(b) the polymer or gum or combination of polymer(s) and/or gum(s) of the shell material is a hydrophilic material having a water solubility of between 2 and 100%.

10. A capsule according to claim 9 wherein the shell material includes at least a relatively hydrophobic polymer and a controlled amount of a hydrophilic secondary polymer.

11. A capsule according to claim 10 wherein the hydrophobic polymer is carrageenan and the secondary polymer is selected from hydroxypropylmethylcellulose or hydroxypropyl starch.

12. A capsule according to claim 11 wherein the amount of carrageenan is in the range of from about 6 to 12 % by weight of the wet shell composition.

13. A capsule according to any one of claim 11 wherein the ratio between the carrageenan and the secondary polymer ranges from about 1:1 to about 1:4.

14. A capsule according to anyone of claim 13 wherein the carrageenan is either iota, lambda or kappa carrageenan.

15. A capsule according to claim 1 wherein;

(a) the migratable component(s) of the fill material is/are hydrophobic, having a water solubility of less than 0.5%; and

(b) the shell composition is a cellulose derivative in combination with a secondary polymer to provide a composition which is hydrophilic in nature having a water solubility of from 2 to 100%.

16. A capsule according to claim 15 wherein the secondary polymer is guar gum and the fill material is an oil soluble herbal extract.

17. A capsule according to claim 1 wherein the shell is a soft shell and the composition of the shell material includes a plasticiser.

18. A capsule according to claim 17 wherein the plasticiser is selected from polyhydric alcohols, propylene glycol or polyethylene glycol.

19. A capsule according to claim 17 wherein the plasticiser is included in up to 60 weight % of the dry shell composition or 30 weight % of the wet shell composition.

20. A capsule according to claim 17 further including a buffer.

21. A capsule according to claim 1 wherein the fill material contains aldehydic groups, and the shell material comprises a material that does not contain amino groups.

22. A capsule according to claim 21 wherein the fill material includes an almond extract, and the shell material is selected from one or more of furcellaran, ethyl cellulose and a modified starch.

23. A capsule according to claim 1, wherein the shell material is relatively hydrophilic and is formed by the combination of two or more polymers or gums selected from karaya gum, carrageenan, pectin, starch, dextrins, ghatti gum, guar gum, algin, xanthan gum, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylstarch, hydroxyethylstarch, low methoxypectin, carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, ethylhydroxymethylcellulose, polyvinylpyrrolidine, polyvinylalcohol, carboxyvinylpolymer, carbomer, ethylene oxide polymers, and poloxamer.

24. A capsule according to claim 1, wherein the shell material is relatively hydrophobic and is formed by the combination of two or more polymers or gums selected from tragacanth, locust bean gum, psyllium seed gum, quince seed gum,

agar, furcellaran, karaya gum, carrageenan, pectin, starch, dextrins, ethyl cellulose, microcrystalline cellulose, carboxymethyl, locust bean gum, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylstarch, hydroxyethylstarch, low methoxypectin, polymethylacrylates, polyvinylpyrrolidine, polyvinylalcohol, carboxyvinylpolymer and carbomer.

25. A process for producing a capsule having a gelatin free hard or soft shell, the process comprising:

(a) providing a complementary health or pharmaceutical fill material for encapsulation which has been classified by its hydrophoilic/hydrophobic balance as determined by water solubility, or chemical reactivity characteristics;

(b) forming a shell material from a suitable polymer or gum, or a combination of two or more polymers and/or gums, wherein the shell material is selected such that the hydrophilic/hydrophobic balance and/or chemical characteristics of the shell material is compatible with hydrophilic/hydrophobic and/or the chemical characteristics of the fill material to minimise chemical interaction with the fill material components; and

(c) encapsulating the fill material within the shell material.

26. A process according to claim 25 wherein the water solubility, as determined by the percentage water solubility, of the shell material and the migratable component(s) of the complementary health fill material differs by a factor of at least 2.

27. A process according to claim 25 wherein the water solubility, as determined by the percentage water solubility, of the shell material and the migratable component(s) of the fill material differs by a factor of at least 10.

28. A process according to claim 25 wherein the hydrophilic/hydrophobic balance compatibility between the shell material and fill material is such that the equilibrium partition co-efficient is less than 0.05.

29. A process according.to claim 25 wherein the hydrophilic/hydrophobic balance compatibility between the shell material and fill material is such that the equilibrium partition co-efficient is less than 0.01.

30. A process according to claim 25 wherein the polymer or gum is selected from any natural, semi synthetic or synthetic polymer or gum.

31. A process according to claim 25 wherein;

(a) the migratable component(s) of the fill material is/are relatively hydrophilic having a water solubility of between 2% to 100%; and

(b) the polymer or gum is relatively hydrophobic, or the combination of polymer or gums of the shell material is a relatively hydrophobic material having a water solubility of less than 0.5%.

32. A process according to claim 25 wherein;

(a) the migratable component(s) of the fill material is/are relatively hydrophobic having a water solubility of less than 0.5%; and

(b) the polymer or gum or combination of polymers and/or gums of the shell material is a relatively hydrophilic material having a water solubility of between 2 and 100%.

33. A process according to claim 31 wherein the shell material includes at least a relatively hydrophobic polymer and a controlled amount of a hydrophilic secondary polymer.

34. A process according claim 33 wherein the hydrophobic polymer is carrageenan and the secondary polymer is selected from hydroxypropylmethylcellulose or hydroxypropyl starch.

35. A process according claim 33 wherein the amount of carrageenan is in the range of from about 6 to 12 % by weight of the wet shell composition.

36. A process according to claim 34 wherein the ratio between the carrageenan and the secondary polymer ranges from about 1:1 to about 1:4.

37. A process according to claim 34 wherein the carrageenan may incorporate different proportions of iota, lambda or kappa carrageenan.

38. A process according to claim 25 wherein;

(a) the migratable component(s) of the fill material is/are hydrophobic, having a water solubility of less than 0.5%; and

(b) the shell composition is a cellulose derivative in combination with a secondary polymer to provide a composition which is hydrophilic in nature having a water solubility of from 2 to 100%.

39. A process according claim 38 wherein the secondary polymer is guar gum and the fill material is an oil soluble herbal extract.

40. A process according to claim 35 wherein the shell is a soft shell and the composition of the shell material includes a plasticiser.

41. A process according to claim 40 wherein the plasticiser is selected from polyhydric alcohols, propylene glycol or polyethylene glycol.

42. A process according to claim 41 wherein the plasticiser is included in up to 60 weight % of the dry shell composition or 30 weight % of the wet shell composition.

43. A process according to claim 25 wherein the fill material comprises one or more vitamin, mineral, herbal extracts, nutrient or probiotic complementary health products.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU02/00979

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. 7: A61K 9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT, CHEMICAL ABSTRACTS and Keywords

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	AU 55429/01 A (UNION CARBIDE CHEMICALS AND PLASTICS TECHNOLOGY CORPORATION) 2 May 2002 Page 1 line 23 to page 2 line 8, example 7 and the claims	1-7,9,17-19,21,23,25-30,40-42
X	Derwent Abstract Accession No. 2001-204256/21, Class A96 B07, EP 1072258 A (GREITHER) 31 January 2001 Abstract	1-7,9,23,25-30,32
X	WO 01/03677 A (R.P SCHERER TECHNOLOGIES, INC) 18 January 2001 Page 5 lines 4-11, page 12 lines4-10 and table 1, claims 1 and 2	1-8,10-14,17-21,24-31,33-37,40-42

[X] Further documents are listed in the continuation of Box C   [X] See patent family annex

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 714656 B (SHIONOGI QUALICAPS CO LTD) 5 June 1996 Page 1 lines 13-18, page 3 lines 10-15 and 55-57	1-7,9,15,23, 25-30,32,38
X	US 5342626 A (WINSTON et al) 30 August 1994 Column 1 lines 13-26, 46-50, column 2 lines 22-50, column 3 lines67,68 and example 9	1-10,12-14, 17-21,22-33, 35-37,40-42
X	US 4917885 A (CHIBA et al) 17 April 1990 Column 1 lines 20-35, column 2 lines 22-52, column 4 line 60, column 7 examples 1,2,3 and column 8 example 6	1-10,15,17-19,21,23-33,38,40-42
X	Patent Abstracts of Japan, JP, 63-164858 A (UNIE KOROIDO KK) 8 July 1988 Abstract	1-8,10-14,23,25-31,33-37

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	55429/01	WO	2002/07711				
WO	2001/03677	AU	60715/00	BR	200011489	EP	1105107
		NO	20020055	US	6340473		
EP	714656	JP	8208458	US	5756123		
US	5342626	AU	60676/94	CA	2121555	EP	622408
		JP	6329833				
US	4917885	AU	43183/85	CA	1256797	CN	85106760
		EP	180287	JP	61100519		

END OF ANNEX